A rare case of venous sinus thrombosis and pulmonary embolisms secondary to myomatous erythrocytosis syndrome

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Myomatous erythrocytosis syndrome is a rare phenomenon of secondary polycythemia evolving from uterine leiomyoma. Although the underlying pathology is still unknown, patients have an increased risk of venous thrombosis. A 44-year-old GO (gravida zero) presented with an incidental finding of secondary polycythemia, and a diagnosis of myomatous erythrocytosis syndrome was made because of her large uterine fibroids. She was placed on therapeutic anticoagulation after developing pulmonary embolisms and a dural sinus venous thrombosis. Subsequently, she underwent uterine artery embolization, which resulted in a substantial decrease in her erythropoietin (8.1 mU/mL) along with hemoglobin (15.1 g/dL) and hematocrit (4 5g/dL). Myomatous erythrocytosis syndrome can cause venous thrombosis, leading to neurologic complications. In patients with increased risk for surgery, uterine artery embolization is an effective option for treatment.

Key words: myomatous erythrocytosis syndrome, secondary polycythemia, uterine leiomyomas, venous sinus thrombosis

Teaching points

1. Myomatous erythrocytosis syndrome should be included in a differential diagnosis of patients presenting with secondary polycythemia and uterine leiomyomas.
2. Venous thrombosis is a rare but life-threatening condition to consider in myomatous erythrocytosis syndrome.
3. Uterine artery embolization is a viable treatment option for those who prefer alternative management, are at risk of complications with surgery, or desire children in the future.

Introduction

Uterine leiomyomas, or fibroids, are tumors of the myometrium that are commonly diagnosed in females of reproductive age. Although many remain asymptomatic, patients can experience bulk-related symptoms such as pelvic pain, urinary tract or bowel problems, painful intercourse, infertility, myxomatous torsion, and dysmenorrhea and menorrhagia.[1] Researchers have suggested a potential association between venous thromboembolism (VTE) and leiomyomas, attributing this to the mass compressing effects of large fibroids at the iliac veins and inferior vena cava, resulting in venous stasis in the pelvis and lower extremities.[2] Most often, this results in a deep venous thrombosis (DVT) and pulmonary embolism (PE) sequence.[3] Numerous therapies aimed at managing symptoms or addressing the leiomyomas directly are available, but they remain the most frequent indication for hysterectomy in the United States.[1]

Typically, leiomyomas are benign tumors, but there have been cases of autonomous erythropoietin (EPO) producing tumors, which produce EPO independent of oxygen status.[4] EPO is a hormone that is mainly secreted by the kidneys and is essential for the proliferation of red blood cell (RBC) precursors; EPO deficiency can cause anemia, whereas EPO excess can induce secondary polycythemia which increases blood viscosity and can increase the risk of thromboembolism. Secondary polycythemia, or the condition of increased RBC mass because of elevated EPO, has many causes, including inherited mutations, congenital methemoglobinemia, hypoxia, recombinant erythropoiesis-stimulating agents used to enhance athletic performance and autonomous EPO-producing tumors.[5] Such tumors can lead to the development of myomatous erythrocytosis syndrome (MES).

MES is characterized by the presence of uterine leiomyoma and secondary polycythemia, seen with elevated hemoglobin, hematocrit, and serum EPO. The resulting increased RBC mass can result in serious complications related to blood hyperviscosity, including stroke, VTE, and pulmonary hypertension.[6] In a review of the existing literature, there have been 57 cases of MES from 1946 to 2018.[4] Patients with MES present with symptoms associated with

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leiomyomas rather than those related to polycythemia.[4] Surgical resection remains the standard of care for MES; in most cases, EPO levels were observed to return to baseline following removal of the mass.[4] Although leiomyomas alone can result in the DVT to PE sequence because of the compressing effects on nearby vessels, MES can produce consequences at distant sites. We present a unique case of MES that resulted in multiple PE events, and venous sinus thrombosis. To our knowledge, this is the second case that has resulted in VTE in cerebral structures and is evidence that uterus-sparing procedures such as uterine artery embolization can be beneficial in reducing hemoglobin, hematocrit, and serum EPO levels.

Case

A 44-year-old GO Caucasian female presented to a hematologist after an incidental finding of worsening polycythemia. Previously, the patient was coordinating an abdominal hysterectomy with her primary gynecologist for uterine fibroids. At the time of the presentation, she had elevated hemoglobin of 19.4 g/dL and elevated hematocrit of 59.5 g/dL. She reported feeling well and denied any associated symptoms of polycythemia, including headache and blurry vision. She reported being amenorrheic because of her oral contraceptive pill.

Her past medical history included migraines, allergic rhinitis, anxiety, cervical human papillomavirus infection, intramural leiomyoma of the uterus, and premenstrual dysphoric disorder. Her current medications include hydroxyzine, oral contraception, bupropion, and galcanezumab. Her family history was significant for paternal factor V Leiden mutation.

During her hematology appointment, the workup revealed decreased RBC count (6.68 million/mm^3), elevated hemoglobin (19.8 g/dL), elevated hematocrit (59.3 g/dL), and elevated EPO (22.2 mU/mL). Per hematology, the patient was diagnosed with polycythemia secondary to elevated EPO. At this time, the polycythemia was suspected to be due to an EPO-secreting leiomyoma of the uterus. She underwent a therapeutic phlebotomy to reduce her hematocrit.

After receiving 2 therapeutic phlebotomy treatments, she presented to the emergency department with a left-sided headache. The patient reported worsening pain after sneezing, coughing, and bearing down. On chest computed tomography angiography, the patient was found to have pulmonary emboli in the right lower lobe and right middle lobe. On brain MRI without contrast, the patient was found to have a left transverse sigmoid venous sinus thrombosis. At this time, her hemoglobin (17.6 g/dL) and hematocrit (53.5 g/dL) were still elevated. The patient tested negatively for factor V Leiden mutation. The hematologist was consulted, and the patient was placed on rivaroxaban because of her diagnosis of both pulmonary emboli and venous sinus thromboses.

After being discharged from the emergency department, she was seen in the hematology clinic for follow-up. She underwent laboratory testing, and her EPO was higher than in previous laboratory values (24.5 mU/mL). She received counseling regarding the treatment of her uterine fibroids. One month later, she underwent uterine artery embolization for a 22-cm fibroid uterus, and interventional radiology reported a 50% reduction in uterus size. After uterine artery embolization, her EPO was significantly reduced (8.1mU/mL) along with hemoglobin (15.1 g/dL) and hematocrit (45 g/dL).

Despite her labs trending downward and normalizing after the uterine artery embolization, the patient continued to report significant abdominal distension and bloating. She presented to a gynecologic oncologist for her discomfort, and she was found to have a 26-week uterus on an abdominal and bimanual examination. The patient was counseled on surgical management and underwent a total abdominal hysterectomy and bilateral salpingectomy. During surgery, a 2022-gram uterine tumor arising from the posterior cul-de-sac was removed and sent to pathology. The final pathology reported the uterine tumor was benign leiomyomas without evidence of any low-grade sarcoma.

Following her surgery, all her laboratory values, including hemoglobin, hematocrit, and EPO, remained within normal limits. Follow-up imaging showed no evidence of residual thrombus.

Discussion

The incidence of polycythemia secondary to uterine leiomyomas has been reported in the literature but is not a typical presentation for patients. There have been several hypotheses made suggesting autonomous EPO production from the leiomyomata.[6,7] However, the exact pathophysiology remains unclear. Polycythemia inherently causes thrombosis and can lead to a variety of complications, including myocardial infarction, cerebrovascular events, superficial thrombophlebitis, DVTs, and PEs.[1] In addition, it has been well-documented that patients with uterine leiomyomas are susceptible to venous thromboembolism, most commonly deep venous thromboembolism (DVT).[5,8,9] In addition, PEs secondary to uterine leiomyomas have been documented as a rare complication.[5,9] Large-size uteri have been shown to cause compressive effects of the pelvic vasculature, leading to venous stasis leading to both DVTs and PE.[4] Literature of neurologic complications secondary to uterine leiomyomas is exceptionally rare. The literature reveals only one other report of cerebral vein thrombosis secondary to uterine leiomyoma.[10] Our patient's case is exceedingly rare because it presented both PE and cerebral vein thrombosis. Neurologic complications such as cerebral vein thrombosis should be considered, and patients should be counseled on possible symptoms at diagnosis of uterine leiomyomas.

Hysterectomy is currently the gold standard for uterine leiomyomas; however, studies have suggested uterine artery embolization is a viable option. There have been several successful reports of treatment of myomatous erythrocytosis with uterine artery embolization.[11,12] The premise of uterine artery embolization (UAE) is to reduce blood flow to the uterine arteries by placing embolic material through x-ray guidance to induce fibrosis

and necrosis of the fibroids.[13] In this case, UAE successfully improved her laboratory values and successfully treated her MES by reducing hematocrit, hemoglobin, and EPO. It is hypothesized the reduction of blood flow and necrosis to the EPO-secreting fibroid is the mechanism of treatment. However, she continued to complain of abdominal distension and was counseled to have a hysterectomy to reduce her bulk symptoms. After the hysterectomy, the patient had a dramatic postoperative response with no return of bulk symptoms. Other studies have shown significant variability in fibroid volume reduction from 6% to 67% in the UAE.[13] The fibroid's location may play a significant factor, such as serosal or pedunculated serosal tumors are less likely to be successfully treated by UAE.[14,15] This case suggests UAE can be a beneficial uterine-sparing option to reduce the risk of hypercoagulability in MES but was ineffective in reducing overall size and bulk symptoms. Therefore, it is difficult to predict if UAE is a primary treatment option for MES, and more research is required to advance therapeutic interventions.

Traditionally, MES is diagnosed by immunostaining for EPO.[16] Although pathologic sampling and staining were not conducted in this case, the researchers believe that a diagnosis of MES is warranted because the patient's laboratory values significantly dropped following UAE and remained at baseline following the removal of her uterus. It is important to note that this patient was on an oral contraceptive pill, which can increase the risk of VTE and stroke; therefore, OCP (Oral Contraceptive Pill) use must be considered as a possible cofounder.[17] To our knowledge, the patient did not have other hypercoagulable risk factors, as she quit smoking cigarettes in 2016 and tested negative for factor V Leiden.

Careful discussion and education should be had with patients who present with MES. Although rare, it is important to counsel patients on risk factors of thromboembolism, including respiratory and neurologic complications. In addition, patients should be counseled on the possible treatment options, including both hysterectomy and UAE. UAE treatment can be a beneficial uterine-sparing option for those who prefer alternative management, are at risk of complications with surgery, or desire children in the future. ■

CRediT authorship contribution statement

Eleza Valente: Formal analysis, Project administration, Writing – original draft, Writing – review & editing. **Morgan Zueger:** Formal analysis, Writing – original draft, Writing – review & editing. **Daniel Donato:** Supervision, Writing – review & editing. ■

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